Recommendations

	% Concentration	Dose mL	Dose mg	Motor Block
Anesthesia				
for Surgery	0.5–0.75	10–20	50–150	Moderate to complete
for Cesarean	0.5	20–30	100–150	Moderate to complete
Nerve	0.25–0.5	30 0.4 mL/kg	75–150 1–2 mg/kg	Moderate to complete
	0.75	5–15	37.5–112.5	Moderate to complete
Infiltration	0.25	60	150	Not applicable
Management*				
Analgesia (bolus)	0.25	10–20	25–50	Minimal to moderate
Analgesia (infusion)	0.125[b,c]–0.25[c]	4–10 mL/h	5–25 mg/h	Minimal to moderate

management Chirocaine® can be used epidurally with fentanyl or clonidine.
is to be used only as adjunct therapy in combination with fentanyl or clonidine.
of Chirocaine standard solutions should be made with preservative free 0.9% saline according to standard hos- procedures for sterility.

chemical disinfection of the container surface is de- ether isopropyl alcohol (91%) or ethyl alcohol (70%) is mended. It is recommended that chemical disinfection complished by wiping the vial stopper thoroughly with gauze that has been moistened with the recom- alcohol) just prior to use.

container is required to have a sterile outside, glass may be autoclaved once. Stability has been dem- following an autoclave cycle at 121°C for 15 min-

risk of contamination, the drug product should be IMMEDIATELY if the vial stopper is removed. The are intended for single use and do not contain servatives; any solution remaining from an open con- should be discarded.

aseptic techniques and procedures, refer to standard laboratory textbooks.

Chirocaine Compatibility and Admixtures

Chirocaine may not be compatible with alkaline solutions of pH greater than 8.5. Studies have shown that Chirocaine is compatible with 0.9% Sodium Chloride Injection, USP and with saline solutions containing fentanyl or clonidine. Compatibility studies with other parenteral drugs have not been studied.

Stability

Chirocaine® diluted in 0.9% Sodium Chloride Injection is physically and chemically stable when stored in PVC (polyvinyl chloride) bags at ambient room temperature for up to 24 hours. Aseptic techniques should be used to prepare the admixture product. Admixtures of Chirocaine should be prepared for single patient use only and used within 24 hours of preparation. The unused portion of diluted Chirocaine should be discarded after each use.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions that are cloudy and colorless should not be used.

(see table above)

The dosages in the table are those considered to be necessary to produce a successful block and should be regarded as guidelines for use in adults. Individual variations in onset and duration of block may occur.

Epidural doses of up to 375 mg have been administered intravenously to patients during a surgical procedure.

The maximum dose in 24 hours for intraoperative block and post-operative pain management was 695 mg.

The maximum dose administered as a post-operative epidural infusion over 24 hours was 570 mg.

The maximum dose administered to patients as a single brachial plexus injection was 300 mg for brachial plexus block.

HOW SUPPLIED

2.5 mg/mL (0.25% levobupivacaine).
Multiple-Dose Vials. (NDC 59011-997-10)
Single-Dose Vials. (NDC 59011-997-30)
5 mg/mL (0.5% levobupivacaine).
Single-Dose Vials. (NDC 59011-998-10)
Single-Dose Vials. (NDC 59011-998-30)
7.5 mg/mL (0.75% levobupivacaine).
Single-Dose Vials. (NDC 59011-999-10)
Single-Dose Vials. (NDC 59011-999-30)

Chirocaine at controlled room temperature, 20°–25°C excursions permitted to 15°–30°C (59°–86°F).

Manufactured by:
Abbott Laboratories, Inc.
Abbott Park, IL 60064-6146

Distributed by:
Purdue Pharma L.P.
Stamford, CT 06901-3431

Patent Numbers:
5,472,124; 5,786,484; 5,849,763; 5,919,804

12/2001

OT00341A
300062-0D-001

Shown in Product Identification Guide, page 331

OXYCONTIN®

(Oxycodone HCl Controlled-Release) Tablets
10 mg 20 mg 40 mg 80 mg* 160 mg*

*80 mg and 160 mg for use in opioid-tolerant patients only

WARNING:

OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

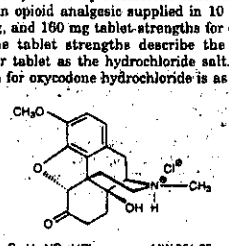
OxyContin Tablets are NOT intended for use as a prn analgesic.

OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

DESCRIPTION

OxyContin® (oxycodone hydrochloride controlled-release) Tablets are an opioid analgesic supplied in 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



$C_{18}H_{21}NO_4$•HCl MW 351.83

The chemical formula is 4, 5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7). The tablets contain the following inactive ingredients: ammonio methacrylate copolymer, hydroxypropyl methylcellulose, lactose, magnesium stearate, povidone, red iron oxide (20 mg strength tablet only), stearyl alcohol, talc, titanium dioxide, triacetin, yellow iron oxide (40 mg strength tablet only), yellow iron oxide with FD&C blue No. 2 (80 mg strength tablet only), FD&C blue No. 2 (160 mg strength tablet only) and other ingredients.

CLINICAL PHARMACOLOGY

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Central Nervous System

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of OxyContin® overdose (See OVERDOSAGE).

Gastrointestinal Tract And Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration—Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall "drug effect", analgesia and feelings of "relaxation".

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients must be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration—Adverse Experience Relationships

OxyContin® Tablets are associated with typical opioid-related adverse experiences. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is not clinically relevant.

As with all opioids, the dose must be individualized (see DOSAGE AND ADMINISTRATION), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

PHARMACOKINETICS AND METABOLISM

The activity of OxyContin Tablets is primarily due to the parent drug oxycodone. OxyContin Tablets are designed to provide controlled delivery of oxycodone over 12 hours.

Breaking, chewing or crushing OxyContin Tablets eliminates the controlled delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from OxyContin Tablets is pH independent. Oxycodone is well absorbed from OxyContin Tablets with an oral bioavailability of 60% to 87%. The relative oral bioavailability of OxyContin to immediate-release oral dosage forms is 100%. Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24–36 hours. Dose proportionality and/or bioavailability has been established for the 10 mg, 20 mg,

Continued on next page

Oxycontin—Cont.

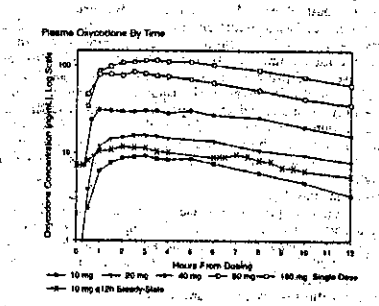
40 mg, 80 mg, and 160 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of OxyContin® was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. In normal volunteers, the t½ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, OxyContin Tablets exhibit a biphasic absorption pattern with two apparent absorption half-times of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

Plasma Oxycodone by Time

Dose proportionality has been established for the 10 mg, 20 mg, 40 mg, and 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 1 below). Another study established that the 160 mg tablet is bioequivalent to 2 × 80 mg tablets as well as to 4 × 40 mg for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 2 below). Given the short half-life of elimination of oxycodone from OxyContin®, steady-state plasma concentrations of oxycodone are achieved within 24–36 hours of initiation of dosing with OxyContin Tablets. In a study comparing 10 mg of OxyContin every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations. There was less fluctuation in plasma concentrations for the OxyContin Tablets than for the immediate-release formulation.



[See table 1 above]

[See table 2 above]

OxyContin® is NOT INDICATED FOR RECTAL ADMINISTRATION. Data from a study involving 21 normal volunteers show that OxyContin Tablets administered per rectum resulted in an AUC 39% greater and a C_{max} 8% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from OxyContin. However, the peak plasma concentration of oxycodone increased by 25% when a OxyContin 160 mg Tablet was administered with a high-fat meal.

Distribution

Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk (see PRECAUTIONS).

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

The formation of oxymorphone, but not noroxycodone, is mediated by cytochrome P450 2D6 and, as such, its formation can, in theory, be affected by other drugs (see Drug-Drug Interactions).

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤ 14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

TABLE 1
Mean (% coefficient variation)

Regimen/ Dosage Form	AUC (ng·hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)
Single Dose			
10 mg OxyContin	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]
20 mg OxyContin	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]
40 mg OxyContin	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]
80 mg OxyContin*	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]
Multiple Dose			
10 mg OxyContin Tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]
5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]

TABLE 2
Mean (% coefficient variation)

Regimen/ Dosage Form	AUC (ng·hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)
Single Dose			
4×40 mg OxyContin*	1935.3 [34.7]	152.0 [28.9]	2.56 [42.3]
2×80 mg OxyContin*	1859.3 [30.1]	153.4 [25.1]	2.78 [69.5]
1×160 mg OxyContin*	1866.4 [30.5]	156.4 [24.8]	2.54 [36.4]

†for single-dose AUC=$AUC_{0\text{-}inf}$, for multiple-dose AUC=$AUC_{0\text{-}\tau}$
*data obtained while volunteers received naltrexone which can enhance absorption.

Special Populations

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in t½ of elimination for oxycodone of only 1 hour (see PRECAUTIONS).

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The t½ elimination for oxycodone increased by 2.3 hours (see PRECAUTIONS).

Drug-Drug Interactions (see PRECAUTIONS)

Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone which represents less than 15% of the total administered dose. This route of elimination may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants). However, in a study involving 10 subjects using quinidine, a known inhibitor of cytochrome P450 2D6, the pharmacodynamic effects of oxycodone were unchanged.

Pharmacodynamics

A single-dose, double-blind, placebo- and dose-controlled study was conducted using OxyContin® (10, 20, and 30 mg) in an analgesic pain model involving 182 patients with moderate to severe pain. Twenty and 30 mg of OxyContin were superior in reducing pain compared with placebo, and this difference was statistically significant. The onset of analgesic action with OxyContin occurred within 1 hour in most patients following oral administration.

CLINICAL TRIALS

A double-blind placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 183 patients with chronic, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, 20 mg OxyContin q12h but not 10 mg OxyContin q12h decreased pain compared with placebo, and this difference was statistically significant.

INDICATIONS AND USAGE

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. OxyContin is NOT intended for use as a prn analgesic.

Physicians should individualize treatment in every case, initiating therapy at the appropriate step, when progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids is indicated of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society Guidelines. OxyContin is not indicated for pain in the immediate postoperative period (the first 12–24 hours following surgery) if the pain is mild, or not expected to persist for an extended period of time. OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

CONTRAINDICATIONS

OxyContin® is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin is contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCONTIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids. Even OxyContin 80 mg and 160 mg Tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more for the 80 mg tablet, or 320 mg or more for the 160 mg tablet. Care should be taken in the prescribing of these tablet strengths. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Misuse, Abuse and Diversion of Opioids

Oxycodone is an opioid agonist of the morphine type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Drug abuse of OxyContin has been reported as being associated with chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see WARNINGS—Drug ABUSE AND ADDICTION).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The

addiction to opioid analgesics in properly managed pa-
with pain has been reported to be rare. However, data
available to establish the true incidence of addiction
chronic pain patients.

healthcare professionals should contact their State Profes-
Licensing Board, or State Controlled Substances Au-
for information on how to prevent and detect abuse
diversion of this product.

Precautions with Alcohol and Drugs of Abuse

oxycodone may be expected to have additive effects when
used in conjunction with alcohol, other opioids, or illicit
drugs that cause central nervous system depression.

DRUG ABUSE AND ADDICTION

OxyContin® is a mu-agonist opioid with an abuse liability
similar to morphine and is a Schedule II controlled sub-
stance. Oxycodone, like morphine and other opioids used
for analgesia, can be abused and is subject to criminal
diversion.

Drug addiction is characterized by compulsive use, use for
non-medical purposes, and continued use despite harm or
risk of harm. Drug addiction is a treatable disease, utilizing
a multi-disciplinary approach, but relapse is common.

"Drug-seeking" behavior is very common in addicts and
drug abusers. Drug-seeking tactics include emergency calls
or visits near the end of office hours, refusal to undergo ap-
propriate examination, testing or referral, repeated "loss" of
prescriptions, tampering with prescriptions and reluctance
to provide prior medical records or contact information for
other treating physician(s). "Doctor shopping" to obtain ad-
ditional prescriptions is common among drug abusers and
people suffering from untreated addiction.

Drug abuse and addiction are separate and distinct from physical
dependence and tolerance. Physicians should be aware that
addiction may not be accompanied by concurrent tolerance
and symptoms of physical dependence in all addicts. In
addition, abuse of opioids can occur in the absence of true
addiction and is characterized by misuse for non-medical
purposes, often in combination with other psychoactive sub-
stances. OxyContin, like other opioids, has been diverted for
non-medical use. Careful record-keeping of prescribing in-
formation, including quantity, frequency, and renewal re-
quests is strongly advised.

Proper assessment of the patient, proper prescribing prac-
tices, periodic re-evaluation of therapy, and proper dispens-
ing and storage are appropriate measures that help to limit
abuse of opioid drugs.

OxyContin consists of a dual-polymer matrix, intended for
oral use only. **Abuse of the crushed tablet poses a hazard of
overdose and death. This risk is increased with concurrent
abuse of alcohol and other substances. With parenteral
abuse, the tablet excipients, especially talc, can be ex-
pected to result in local tissue necrosis, infection, pulmo-
nary granulomas, and increased risk of endocarditis and
valvular heart injury. Parenteral drug abuse is commonly
associated with transmission of infectious diseases such as
hepatitis and HIV.**

Respiratory Depression

Respiratory depression is the chief hazard from oxycodone,
the active ingredient in OxyContin®, as with all opioid ago-
nists. Respiratory depression is a particular problem in el-
derly or debilitated patients, usually following large initial
doses in non-tolerant patients, or when opioids are given in
conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients
with significant chronic obstructive pulmonary disease or
cor pulmonale, and in patients having a substantially de-
creased respiratory reserve, hypoxia, hypercapnia, or pre-
existing respiratory depression. In such patients, even
therapeutic doses of oxycodone may decrease respira-
tory drive to the point of apnea. In these patients alterna-
tive non-opioid analgesics should be considered, and opioids
should be employed only under careful medical supervision
at the lowest effective dose.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of opioids include carbon
dioxide retention and secondary elevation of cerebrospinal
fluid pressure, and may be markedly exaggerated in the
presence of head injury, intracranial lesions, or other
causes of pre-existing increased intracranial pressure.
Oxycodone produces effects on pupillary response and con-
sciousness which may obscure neurologic signs of further in-
crease in intracranial pressure in patients with head inju-
ries.

Hypotensive Effect

Oxycodone may cause severe hypotension. There is an
added risk to individuals whose ability to maintain blood
pressure has been compromised by a depleted blood volume,
or after concurrent administration with drugs such as phe-
nothiazines or other agents which compromise vasomotor
tone. Oxycodone may produce orthostatic hypotension in
ambulatory patients. Oxycodone, like all opioid analgesics
and the morphine-type, should be administered with caution
to patients in circulatory shock, since vasodilation produced
by the drug may further reduce cardiac output and blood
pressure.

PRECAUTIONS

General

Opioid analgesics have a narrow therapeutic index in cer-
tain patient populations, especially when combined with
other depressant drugs, and should be reserved for cases
where the benefits of opioid analgesia outweigh the known
risks of respiratory depression, altered mental state, and
hypotension.

Use of OxyContin® is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with other CNS Depressants

OxyContin should be used with caution and started in a reduced dosage ($^1/_3$ to $^1/_2$ of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of OxyContin.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery and Postoperative Use

OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain).

OxyContin is not indicated for pain in the immediate postoperative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

OxyContin is not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time.

OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (See American Pain Society guidelines).

Patients who are already receiving OxyContin® Tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (see DOSAGE AND ADMINISTRATION).

OxyContin and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common postoperative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in postoperative patients receiving opioids. Standard supportive therapy should be implemented.

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see DOSAGE AND ADMINISTRATION: Cessation of Therapy).

Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin Tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that OxyContin Tablets contain oxycodone, which is a morphine-like substance.
2. Patients should be advised that OxyContin Tablets were designed to work properly only if swallowed whole. OxyContin Tablets will release all their contents at once if broken, chewed, or crushed, resulting in a risk of fatal overdose.
3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
4. Patients should be advised not to adjust the dose of OxyContin® without consulting the prescribing professional.
5. Patients should be advised that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
6. Patients should not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
8. Patients should be advised that OxyContin is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
9. Patients should be advised that they may pass empty matrix "ghosts" (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.
10. Patients should be advised that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
11. Patients should be instructed to keep OxyContin in a secure place out of the reach of children. When OxyContin is no longer needed, the unused tablets should be destroyed by flushing down the toilet.

Use in Drug and Alcohol Addiction

OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including OxyContin®, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

OxyContin, like all opioid analgesics, should be started at $^1/_3$ to $^1/_2$ of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of oxycodone to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 µg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 µg/mL and with activation 48 hours after exposure at doses of up to 5000 µg/mL, and in the in vivo bone marrow micronucleus test in mice (at plasma levels of up to 48 µg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 µg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation.

Pregnancy

Teratogenic Effects—Category B. Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

OxyContin® is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Continued on next page

Oxycontin—Cont.

Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use

Safety and effectiveness of OxyContin have not been established in pediatric patients below the age of 18. It must be remembered that OxyContin Tablets cannot be crushed or divided for administration.

Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% (see PHARMACOKINETICS AND METABOLISM). Of the total number of subjects (445) in clinical studies of OxyContin, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in the elderly patients who received OxyContin. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to $^1/_3$ to $^1/_2$ of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Hepatic Impairment

A study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at $^1/_3$ to $^1/_2$ the usual doses and careful dose titration is warranted.

Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS

The safety of OxyContin® was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OxyContin in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Serious adverse reactions which may be associated with OxyContin Tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension, or shock (see OVERDOSAGE).

The non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as OxyContin therapy is continued and some degree of tolerance is developed.

Clinical trials comparing OxyContin with immediate-release oxycodone and placebo revealed a similar adverse event profile between OxyContin and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

TABLE 3

	OxyContin (n=227) (%)	Immediate-Release (n=225) (%)	Placebo (n=45) (%)
Constipation	(23)	(26)	(7)
Nausea	(23)	(27)	(11)
Somnolence	(23)	(24)	(4)
Dizziness	(13)	(16)	(9)
Pruritus	(13)	(12)	(2)
Vomiting	(12)	(14)	(7)
Headache	(7)	(8)	(7)
Dry Mouth	(6)	(7)	(2)
Asthenia	(6)	(7)	–
Sweating	(5)	(6)	(2)

The following adverse experiences were reported in OxyContin®-treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in post-marketing experience.

General: accidental injury, chest pain, facial edema, malaise, neck pain, pain

Cardiovascular: migraine, syncope, vasodilation, ST depression

Digestive: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis, ileus

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropriate antidiuretic hormone secretion, thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, seizures, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome with or without seizures

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis, urticaria

Special Senses: abnormal vision, taste perversion

Urogenital: amenorrhea, decreased libido, dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Deaths due to overdose have been reported with abuse and misuse of OxyContin®, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when OxyContin is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including OxyContin, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

DOSAGE AND ADMINISTRATION

General Principles

OXYCONTIN IS AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE WITH AN ABUSE LIABILITY SIMILAR TO MORPHINE. OXYCODONE, LIKE MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA, CAN BE ABUSED AND IS SUBJECT TO CRIMINAL DIVERSION.

OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCONTIN® TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

One OxyContin 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high-fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets (see DOSAGE AND ADMINISTRATION).

In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's [illegible] pain and side effects and the health professional's judgment.

OxyContin Tablets are a controlled-release oral [illegible] of oxycodone hydrochloride indicated for the [illegible] moderate to severe pain when a continuous around-the-clock analgesic is needed for an extended period of time. The controlled-release nature of the formulation allows OxyContin to be effectively administered every 12 hours (see CLINICAL PHARMACOLOGY, PHARMACOKINETICS AND METABOLISM). While symmetrical dosing (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Physicians should individualize treatment [illegible] sive plan of pain management such as outlined by the World Health Organization, the American Pain Society, and the Federation of State Medical Boards. Most Comprehensive Health care professionals should follow the appropriate pain management principles of careful assessment of the patient, monitoring [See BOXED WARNING].

Initiation of Therapy

It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's [illegible] and non-opioid analgesic treatment. Attention should be given to:

(1) the general condition and medical status of the patient;
(2) the daily dose, potency, and kind of the analgesic the patient has been taking;
(3) the reliability of the conversion estimate used to calculate the dose of oxycodone;
(4) the patient's opioid exposure and opioid tolerance (if any);
(5) special safety issues associated with converting to OxyContin® doses at or exceeding 160 mg q12h (see Special Instructions for OxyContin 80 mg and 160 mg Tablets); and
(6) the balance between pain control and different adverse experiences.

Care should be taken to use low initial doses of OxyContin in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see PRECAUTIONS: Drug-Drug Interactions).

For initiation of OxyContin therapy for patients previously taking opioids, the conversion ratios from Poley and Slattery [NEJM, 1985; 313:84–95], found below, are a reasonable starting point, although not verified in well-controlled multiple-dose trials.

Experience indicates a reasonable starting dose of OxyContin for patients who are taking non-opioid analgesics and require continuous around-the-clock therapy for an extended period of time is 10 mg q12h. If adequate analgesic is being provided, it may be continued. OxyContin should be individually titrated to a dose that provides adequate analgesia and minimizes side effects.

1. Using standard conversion ratio estimates (see Table 4 below), multiply the mg/day of the previous opioid by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.
2. When converting from oxycodone, divide the total oral oxycodone dose in half to obtain the twice a day dose of OxyContin.
3. Round down to a dose which is appropriate for the available strengths available (10 mg, 20 mg, 40 mg, 80 mg, 160 mg tablets).
4. Discontinue all other around-the-clock opioid drugs when OxyContin therapy is initiated.
5. No fixed conversion ratio is likely to be satisfactory for all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 4 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

TABLE 4

Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone (Mg/Day Prior Opioid × Factor = Mg/Day Oral Oxycodone)

	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	
Codeine	0.15	
Hydrocodone	0.9	
Hydromorphone	4	20
Levorphanol	7.5	
Meperidine	0.1	
Methadone	1.5*	
Morphine	0.5	

*To be used only for conversion to oral oxycodone in patients receiving high-dose parenteral opioids. For example, conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as the multiplication factor.

In all cases, supplemental analgesia (see below) should be made available in the form of a suitable short-acting analgesic.

...Contin® can be safely used concomitantly with usual ...of non-opioid analgesics and analgesic adjuvants; pro... care is taken to select a proper initial dose (see PRE...CRIPTION...).

...sion from Transdermal Fentanyl to OxyContin

...hours following the removal of the transdermal ...patch, OxyContin treatment can be initiated. Al... there has been no systematic assessment of such ...conservative oxycodone dose, approximately ...12h of OxyContin, should be initially substituted for ...mg/hr fentanyl transdermal patch. The patient ...be followed closely for early titration, as there is very ...clinical experience with this conversion.

...g Expected Opioid Adverse Experiences

...patients receiving opioids, especially those who are ...ive, will experience side effects. Frequently the ...cts from OxyContin are transient, but may require ...tion and management. Adverse events such as consti... should be anticipated and treated aggressively and ...ically, with a stimulant laxative and/or stool soft... Patients do not usually become tolerant to the consti... effects of opioids.

...oid-related side effects such as sedation and nau... usually self-limited and often do not persist beyond ...few days. If nausea persists and is unacceptable to ...patient, treatment with antiemetics or other modalities ...relieve these symptoms and should be considered.

...receiving OxyContin® may pass an intact matrix ...in the stool or via colostomy. These ghosts contain ...no residual oxycodone and are of no clinical conse...

...ualization of Dosage

...therapy is initiated, pain relief and other opioid effects ...be frequently assessed. Patients should be titrated to ...effect (generally mild or no pain with the regular ...) as more than two doses of supplemental analgesia ...4 hours). Patients who experience breakthrough pain ...require dosage adjustment or rescue medication. Be... steady-state plasma concentrations are approximated ...24 to 36 hours, dosage adjustment may be carried ...every 1 to 2 days. It is most appropriate to increase the ...dose, not the dosing frequency. There is no clinical in... on dosing intervals shorter than q12h. As a guide... for the increase from 10 mg to 20 mg q12h, the ...daily oxycodone dose usually can be increased by 25% ...of the current dose at each increase.

...of excessive opioid-related adverse experiences are ...ed, the next dose may be reduced. If this adjustment ...to inadequate analgesia, a supplemental dose of ...release oxycodone may be given. Alternatively, ...oxycodone analgesic adjuvants may be employed. Dose ad... should be made to obtain an appropriate balance ...pain relief and opioid-related adverse experiences. ...significant adverse events occur before the therapeutic ...of mild or no pain is achieved, the events should be ...addressed aggressively. Once adverse events are under control, ...titration should continue to an acceptable level of ...control.

...periods of changing analgesic requirements, includ... initial titration, frequent contact is recommended be... physician, other members of the healthcare team, the ...and the caregiver/family.

...Instructions for OxyContin 80 mg and 160 mg Tab...

...for use in opioid-tolerant patients only.)

...Contin 80 mg and 160 mg Tablets are for use only in ...oid-tolerant patients requiring daily oxycodone equiva... dosages of 160 mg or more for the 80 mg tablet and ...mg or more for the 160 mg tablet. Care should be taken ...the prescribing of these tablet strengths. Patients should ...instructed against use by individuals other than the pa... for whom it was prescribed, as such inappropriate use ...have severe medical consequences, including death.

...OxyContin® 160 mg tablet is comparable to two ...mg tablets when taken on an empty stomach. With a ...fat meal, however, there is a 25% greater peak plasma ...concentration following one 160 mg tablet. Dietary caution ...should be taken when patients are initially titrated to ...mg tablets.

...mental Analgesia

...patients given around-the-clock therapy with con... release opioids may need to have immediate-release ...analgesic available for exacerbations of pain or to prevent ...that occurs predictably during certain patient activi... (incident pain).

...nance of Therapy

...ment of the titration period is to establish a patient-...specific q12h dose that will maintain adequate analgesia ...with acceptable side effects for as long as pain relief is nec... Should pain recur then the dose can be incremen... increased to re-establish pain control. The method of ...adjustment outlined above should be employed to ...establish pain control.

...chronic therapy, especially for non-cancer pain syn... the continued need for around-the-clock opioid ...therapy should be reassessed periodically (e.g., every 6 to 12 ...months) as appropriate.

...ation of Therapy

...the patient no longer requires therapy with ...OxyContin Tablets, doses should be tapered gradually to ...prevent signs and symptoms of withdrawal in the physically ...dependent patient.

...version from OxyContin to Parenteral Opioids

...avoid overdose, conservative dose conversion ratios ...should be followed.

SAFETY AND HANDLING

OxyContin Tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

OxyContin has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

HOW SUPPLIED

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 10 mg are round, unscored, white-colored, convex tablets bearing the symbol OC on one side and 10 on the other. They are supplied as follows:

NDC 59011-100-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-100-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 20 mg are round, unscored, pink-colored, convex tablets bearing the symbol OC on one side and 20 on the other. They are supplied as follows:

NDC 59011-103-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-103-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 40 mg are round, unscored, yellow-colored, convex tablets bearing the symbol OC on one side and 40 on the other. They are supplied as follows:

NDC 59011-105-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-105-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 80 mg are round, unscored, green-colored, convex tablets bearing the symbol OC on one side and 80 on the other. They are supplied as follows:

NDC 59011-107-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-107-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 160 mg are caplet-shaped, unscored, blue-colored, convex tablets bearing the symbol OC on one side and 160 on the other. They are supplied as follows:

NDC 59011-109-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-109-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

Store at 25°C (77°F); excursions permitted between 15°–30°C (59°–86°F).

Dispense in tight, light-resistant container.

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

CAUTION

DEA Order Form Required.

January 25, 2002
OT00367A 300514-0A-001

PATIENT INFORMATION

OXYCONTIN®ⓘ

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

OxyContin® Tablets, 10 mg
OxyContin® Tablets, 20 mg
OxyContin® Tablets, 40 mg
OxyContin® Tablets, 80 mg
OxyContin® Tablets, 160 mg

Read this information carefully before you take OxyContin® (ox-e-CON-tin) tablets. Also read the information you get with your refills. There may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. Only you and your doctor can decide if OxyContin is right for you. Share the important information in this leaflet with members of your household.

What Is The Most Important Information I Should Know About OxyContin®?

- **Use OxyContin the way your doctor tells you to.**
- **Use OxyContin only for the condition for which it was prescribed.**
- **OxyContin is not for occasional ("as needed") use.**
- **Swallow the tablets whole.** Do not break, crush, dissolve, or chew them before swallowing. OxyContin® works properly over 12 hours only when swallowed whole. **If a tablet is broken, crushed, dissolved, or chewed, the entire 12 hour dose will be absorbed into your body all at once. This can be dangerous, causing an overdose, and possibly death.**
- **Keep OxyContin® out of the reach of children.** Accidental overdose by a child is dangerous and may result in death.
- **Prevent theft and misuse.** OxyContin contains a narcotic painkiller that can be a target for people who abuse prescription medicines. Therefore, keep your tablets in a secure place, to protect them from theft. Never give them to anyone else. Selling or giving away this medicine is dangerous and against the law.

What is OxyContin®?

OxyContin® is a tablet that comes in several strengths and contains the medicine oxycodone (ox-e-KOE-done). This medicine is a painkiller like morphine. OxyContin treats moderate to severe pain that is expected to last for an extended period of time. Use OxyContin regularly during treatment. It contains enough medicine to last for up to twelve hours.

Who Should Not Take OxyContin®?

Do not take OxyContin® if

- your doctor did not prescribe OxyContin® for you.
- your pain is mild or will go away in a few days.
- your pain can be controlled by occasional use of other painkillers.
- you have severe asthma or severe lung problems.
- you have had a severe allergic reaction to codeine, hydrocodone, dihydrocodeine, or oxycodone (such as Tylox, Tylenol with Codeine, or Vicodin). A severe allergic reaction includes a severe rash, hives, breathing problems, or dizziness.
- you had surgery less than 12–24 hours ago and you were not taking OxyContin just before surgery.

Your doctor should know about all your medical conditions before deciding if OxyContin is right for you and what dose is best. Tell your doctor about all of your medical problems, especially the ones listed below:

- trouble breathing or lung problems
- head injury
- liver or kidney problems
- adrenal gland problems, such as Addison's disease
- convulsions or seizures
- alcoholism
- hallucinations or other severe mental problems
- past or present substance abuse or drug addiction

If any of these conditions apply to you, and you haven't told your doctor, then you should tell your doctor before taking OxyContin.

If you are pregnant or plan to become pregnant, talk with your doctor. OxyContin may not be right for you. **Tell your doctor if you are breast feeding.** OxyContin will pass through the milk and may harm the baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. They may cause serious medical problems when taken with OxyContin, especially if they cause drowsiness.

How Should I Take OxyContin®?

- **Follow your doctor's directions exactly.** Your doctor may change your dose based on your reactions to the medicine. Do not change your dose unless your doctor tells you to change it. Do not take OxyContin more often than prescribed.
- **Swallow the tablets whole. Do not break, crush, dissolve, or chew before swallowing. If the tablets are not whole, your body will absorb too much medicine at one time. This can lead to serious problems, including overdose and death.**
- **If you miss a dose,** take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless your doctor tells you to.
- **In case of overdose,** call your local emergency number or poison control center right away.
- **Review your pain regularly with your doctor** to determine if you still need OxyContin.
- **You may see tablets in your stools (bowel movements).** Do not be concerned. Your body has already absorbed the medicine.

If you continue to have pain or bothersome side effects, call your doctor.

Stopping OxyContin. Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms. You should not stop taking OxyContin all at once if you have been taking it for more than a few days.

After you stop taking OxyContin, flush the unused tablets down the toilet.

What Should I Avoid While Taking OxyContin®?

- **Do not drive, operate heavy machinery, or participate in any other possibly dangerous activities** until you know how you react to this medicine. OxyContin can make you sleepy.
- **Do not drink alcohol while using OxyContin. It may increase the chance of getting dangerous side effects.**
- **Do not take other medicines without your doctor's approval.** Other medicines include prescription and non-prescription medicines, vitamins, and supplements. Be especially careful about products that make you sleepy.

What are the Possible Side Effects of OxyContin®?

Call your doctor or get medical help right away if

- your breathing slows down
- you feel faint, dizzy, confused, or have any other unusual symptoms

Some of the common side effects of OxyContin® are nausea, vomiting, dizziness, drowsiness, constipation, itching, dry mouth, sweating, weakness, and headache. Some of these side effects may decrease with continued use.

There is a risk of abuse or addiction with narcotic painkillers. If you have abused drugs in the past, you may have a higher chance of developing abuse or addiction again while

Continued on next page

Oxycontin—Cont.

using OxyContin. We do not know how often patients with continuing (chronic) pain become addicted to narcotics, but the risk has been reported to be small.

These are not all the possible side effects of OxyContin. For a complete list, ask your doctor or pharmacist.

General Advice About OxyContin

- Do not use OxyContin for conditions for which it was not prescribed.
- Do not give OxyContin to other people, even if they have the same symptoms you have. Sharing is illegal and may cause severe medical problems, including death.

This leaflet summarizes the most important information about OxyContin. If you would like more information, talk with your doctor. Also, you can ask your pharmacist or doctor for information about OxyContin that is written for health professionals.

Rx Only

Purdue Pharma L.P., Stamford, CT 06901-3431

January 25, 2002

OT00367A 300514-0A-001

Shown in Product Identification Guide, page 331

OXYIR® Ⓒ ℞

[ŏx'-ē-ī'-r']

(oxycodone hydrochloride)

Immediate-Release Oral Capsules

5 mg

OXYFAST® Ⓒ ℞

[ŏx-ē-făst']

(oxycodone hydrochloride)

Immediate-Release

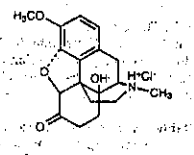
Oral CONCENTRATE Solution*

20 mg/1mL

***This product contains dry natural rubber.**

DESCRIPTION

Oxycodone is 14-hydroxydihydrocodeinone, a white odorless crystalline powder which is derived from the opium alkaloid, thebaine, and may be represented by the following structural formula:



OxyIR® Oral Capsules

Each 5 mg of OxyIR Capsules contains:

Oxycodone hydrochloride ..... 5 mg

Inactive ingredients: Hydroxypropyl methylcellulose, maize starch, polyethylene glycol, polysorbate 80, sucrose, synthetic red iron oxide E172, synthetic yellow iron oxide E172, and titanium dioxide E171.

OxyFast® Oral CONCENTRATE Solution

Each 1 mL of OxyFast Concentrate Solution contains:

Oxycodone hydrochloride ..... 20 mg

Inactive ingredients: citric acid, FD&C yellow No. 10, sodium benzoate, sodium citrate, sodium saccharine, and water.

ACTIONS

The analgesic ingredient, oxycodone, is a semisynthetic narcotic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of oxycodone are analgesia and sedation.

CLINICAL PHARMACOLOGY

Central Nervous System: Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other therapeutic effects of oxycodone include anxiolysis, euphoria, and feelings of relaxation. Like all pure opioid agonists, there is no ceiling effect to analgesia, such as is seen with partial agonists or non-opioid analgesics.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic. Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Gastrointestinal Tract and Other Smooth Muscle: Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary, and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System: Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration—Effect Relationships (PHARMACODYNAMICS): Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects. In normal volunteers these include pupillary constriction, sedation, and overall "drug effect" and in patients, analgesia and feelings of "relaxation." In non-tolerant patients, analgesia is not usually seen at a plasma oxycodone concentration of less than 5–10 ng/mL.

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients need to be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase with repeated dosing due to an increase in pain and/or the development of tolerance.

Concentration—Adverse Experience Relationships: OxyIR Capsules and OxyFast CONCENTRATE Solution are associated with typical opioid-related adverse experiences similar to those seen with all opioids. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is poorly understood.

As with all opioids, the dose must be individualized (see DOSAGE AND ADMINISTRATION), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

INDICATIONS AND USAGE

For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

OxyIR and OxyFast are contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyIR and OxyFast are contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

Respiratory Depression: Respiratory depression is the chief hazard from all opioid agonist preparations. Respiratory depression occurs most frequently in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Hypotensive Effect: OxyIR® Capsules and OxyFast® CONCENTRATE Solution, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. OxyIR and OxyFast may produce orthostatic hypotension in ambulatory patients. OxyIR and OxyFast, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Drug Dependence: Oxycodone can produce drug dependence of the morphine type, and therefore, has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of this drug, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, this drug is subject to the Federal Controlled Substances Act.

Usage in Ambulatory Patients: Oxycodone may impair the mental and/or physical abilities required for the performance of potential hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Interaction with Other Central Nervous System Depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, or other CNS depressants (including alcohol) concomitantly with oxycodone hydrochloride may exhibit additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, this drug should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children: This drug should not be [illegible] to children.

PRECAUTIONS

Special Precautions Regarding OxyFast Oral Concentrate 20 mg/1mL Solution

OxyFast 20 mg/1 mL solution is a highly concentrated solution. Care should be taken in the prescription and dispensing of this solution strength. Patients should be instructed against use by individuals other than the patient, as inappropriate use may cause acute overdosage.

General: Opioid analgesics given on a [illegible] schedule have a narrow therapeutic index in certain patient populations, especially when combined with other CNS depressants and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of OxyIR® and OxyFast® is associated with [illegible] potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary, or renal function; toxic psychosis.

The administration of oxycodone, like all opioid analgesics, may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics: Agonist/antagonist and partial agonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Use in Pancreatic/Biliary Tract Disease: Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of this drug or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Information for Patients/Caregivers: As with any potentially able, patients receiving OxyIR Immediate-Release Capsules or OxyFast CONCENTRATE Solution and caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be advised not to adjust the dose of this drug without consulting the prescribing physician.
2. Patients should be advised that this drug may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving a car or operating heavy machinery).
3. Patients should not combine this drug with alcohol or other central nervous system depressants (including tranquilizers) except by the orders of the physician because additive effects may occur.
4. Women of childbearing potential who are planning to become, pregnant should be advised to consult with a physician regarding the effects of analgesics and narcotic use during pregnancy on themselves and their unborn children.
5. Patients should be advised that this product contains a drug of abuse. They should protect it from theft and it should never be given to anyone other than the patient for whom it was prescribed.
6. Patients should be advised that if they have been taking treatment with this drug for more than a few weeks and cessation of therapy is indicated, it may be necessary to taper this drug dose, rather than abruptly discontinue due to the risk of precipitating withdrawal symptoms. The physician can provide a dose schedule to accomplish gradual discontinuation of the medication.

Laboratory Monitoring: Due to the broad [illegible] concentrations seen in clinical populations, the [illegible] grees of pain, and the development of tolerance, [illegible] codone measurements are usually not helpful in [illegible] management. Plasma concentrations [illegible]